REMARKS

The Office Action dated April 23, 2008 has been received and carefully studied.

The Examiner rejects claims 1-11 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner states that the specification does not enable the various derivatives (hydrates, solvates and prodrug forms) of the compounds of formula (1). The Examiner states that there is no teaching or guidance in the specification regarding any specific solvents used for preparing specific hydrates or solvates and their characterization, and no example present for preparing any specific hydrate or solvate of the compounds of formula (1). The Examiner adds that there is no teaching or guidance in the specification for preparing specific types of prodrug forms such as carboxylic acid esters, amino acid or amide esters, phosphate esters, phosphono esters, sulfate esters, etc. With particular reference to claim 11, the Examiner indicates that claim 11 is enabled for treating colon cancer, but not for cancers in general.

The rejection is respectfully traversed.

"Derivatives" of the compounds of Formula (I) are not claimed in the present application. For example, in claim 5 (claims 1-4 have been cancelled), what is claimed is "a compound of the general formula (I)," said "compound" being called "a high-molecular weight derivative of camptothecins". That is, said "compound" is "a derivative of camptothecins" and having a high-molecular weight," and thus it is surely "a high-molecular weight

derivative of camptothecins". What is claimed in claim 5 are "the compounds of formula (I)" themselves, and not the derivatives (such as hydrates, solvates or prodrug forms) of the compounds of formula (I).

On page 10, lines 8-10 of the specification, "the high-molecular weight derivative of camptothecins of the present invention includes also derivatives showing an effect as a prodrug" is described. This description simply means that among "the high-molecular weight derivatives of camptothecins of the invention" (i.e., "the compounds of formula (I)"), there are derivatives (i.e., the high-molecular weight derivatives of camptothecins), which show an effect as a prodrug. It does not mean some "prodrug forms" of the "compounds of formula (I)".

The same holds true for other claims of the present application. The "derivatives" (such as hydrates, solvates or prodrug form) of "the compounds of general formula (I)" are not claimed in the present application.

With regard to claim 11, as described in the present specification, camptothecin itself is a known antitumor alkaloid suffering from extremely poor solubility in water, and therefore water-soluble derivatives thereof suitable for clinical use have been studied. The present invention provides a solution to this problem of camptothecin as an antitumor alkaloid, and the utility of the present invention should not be limited to the treatment of only colon cancer.

The following table gives the results of *in vivo* tests of the

high-molecular weight derivative of camptothecins of the present invention on the anticancer effects against various human tumor xenografts in nude mice.

The compound used in the tests ("Compound A") is a compound of the general formula (I) wherein R1 is a methyl group, t is approximately 273, A is a trimethylene group, d+e+f is approximately 21, R2 is an ethyl group, R3 is a hydrogen atom, R4 is an isopropylaminocarbonylisopropylamino group, and P is an acetyl group. The tests were carried out after 21 days from administration initiation, according to a similar procedure described in Example 5.

From the results shown in TABLE-A, it is clear that the compound of the present invention, i.e., the high-molecular weight derivative of camptothecins of the general formula (I), has anticancer effects against various human tumors, and therefore is an anticancer agent.

TABLE -A

Anticancer effects against
human tumor xenografts in nude mice

Tumor lines		Drug	Schedule	Dose (mg/kg/day)	T/C (%)
Co-3	human colon cancer	Control	-	0	100
		Compound A	q4d×3	30	6.1
				15	7.5
				7.5	13.1
				3.75	26.6
4-1ST	human gastric cancer	Control	-	0	100
		Compound A	q4d×3	30	0.7
				15	0.7
				7.5	1.7
				3.75	10.9
L-27	human non-small-cell lung cancer	Control	-	0	100
		Compound A	q4d×3	30	0.6
				15	2.5
LX-1	human small cell lung cancer	Control	-	0	100
		Compound A	q4d×3	30	2.2
				15	2.9
				7.5	3.4
				3.75	6.1
AsPC-1	human pancreatic cancer	Control	-	0	100
		Compound A	q4d×3	30	8.0
				15	16.0
				7.5	27.7
VMRC-RCW	human renal cell carcinoma	Control	-	0	100
		Compound A	q4d×3	30	3.9
				15	7.8
				7.5	15.0
				3.75	23.1

*1) q4d×3: administration three times every four days
*2) T/C: Relative tumor volume, Treatment / Control (= no treatment)

The Examiner rejects claims 5, 6 and 9-11 under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner states that the variable "A" in claim 5 is indefinite since no specifics are recited. By the accompanying amendment, claim 5 has been

amended to recite specifics for R1, A, R2, R3, R4 and P. Support for the amendment can be found on page 11, line 22 to page 14, line 26 of the specification, for example. Claim 6 has been amended accordingly, and claim 9 has been cancelled. Claim 10 has been amended by deleting "polymer having a carboxylic acid group at the side chain" and substituting therefore "a polyglutamic acid". Claim 11 has been amended by amending its dependencies.

The Examiner also objects to claims 1-4 and 9-11 for containing non-elected subject matter. By the accompanying amendment, claims 1-4 and 9 have been cancelled without prejudice, and claims 10 and 11 have been amended without prejudice. It is believed that the amendment overcomes the objection.

The Examiner's indication that claims directed to the elected group contain allowable subject matter is noted with appreciation.

Reconsideration and allowance are respectfully requested in view of the foregoing.

Respectfully submitted,

Kevin S. Lemack
Reg. No. 32,579
176 E. Main Street - Suite 5
Westboro, Massachusetts 01581
TEL: (508) 898-1818

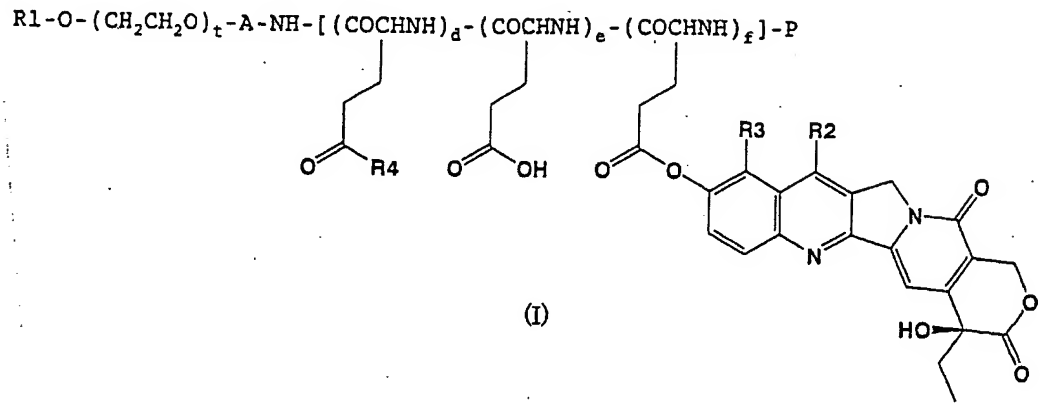
Amendment to the claims

This listing of claims replaced all prior versions, and listings, of claims in the application.

Listing of claims

1-4. (Cancelled)

5. (Currently amended) A high-molecular weight derivative of camptothecins of the general formula (I):



(I)

[wherein, R1 represents a hydrogen atom, methyl group, ethyl group, n-propyl group, i-propyl group, n-butyl group, t-butyl group, benzyl group, 2,2dimethoxyethyl group or 2,2-diethoxyethyl group, ~~or a (C1 to C6) alkyl group optionally having a substituent,~~ t represents an integer of 5 to 11500, A represents a C2 to C6 alkylene group, ~~bonding group,~~ d+e+f represents an

integer of 3 to 200, R2 represents a hydrogen atom, methyl group, ethyl group, dimethylaminomethyl group, 2-[(1-methylethyl)amino]ethyl group, 2-(trimethylsilyl)ethyl group, (4-methyl-1-piperidinyl)methyl group or [(2,3-dideoxy-a-D-erythrohexy-2-enopiranosyl)oxy]methyl group, ~~or a (C1 to C6) alkyl group optionally having a substituent or a silyl group optionally having a substituent,~~ R3 represents a hydrogen atom, methyl group, ethyl group, dimethylaminomethyl group or 2-[(1-methylethyl)amino]ethyl group, ~~or a (C1 to C6) alkyl group optionally having a substituent,~~ R4 may be the same or different and represents methoxy group, ethoxy group, propoxy group, isopropoxy group, benzyloxy group, phenetyloxy group, methylamino group, ethylamino group, propylamino group, isopropylamino group, benzylamino group, acetylamino group, amino acid group having a carboxyl group protected, N,N-dimethylamino group, N,N-diethylamino group, N,N-dipropylamino group, N,N-diisopropylamino group, N,N-dibenzylamino group, N-methyl-N-benzylamino group, methylaminocarbonylmethylamino group, ethylaminocarbonylethylamino group, isopropylaminocarbonylisopropylamino group or cyclohexylaminocarbonylcyclohexylamino group, ~~a (C1 to C20) alkoxyl group optionally having a substituent, a (C1 to C20) alkylamino group optionally having a substituent, a di(C1 to C20) alkylamino group optionally having a substituent or a (C1 to C20) alkylaminocarbonyl (C1 to C20) alkylamino group optionally having a substituent,~~ and P represents a hydrogen atom, formyl group, acetyl group, propionyl group, pivaloyl group, methoxycarbonyl

group, ethoxycarbonyl group or t-butoxycarbonyl group ~~a (C1 to C6) acyl group or a (C1 to C6) alkoxycarbonyl group.~~].

6. (Currently amended) The high-molecular weight derivative of camptothecins according to claim 5, wherein ~~R1 is a (C1 to C4) alkyl group optionally having a substituent,~~ t is an integer of 100 to 300, ~~A is a (C2 to C6) alkylene group,~~ d+e+f is an integer of 6 to 60, the ratio of d is 0 to 60%, the ratio of e is 0 to 60% and the ratio of f is 1 to 100% based on d+e+f~~, R2 is a hydrogen atom or a (C1 to C4) alkyl group optionally having a substituent, R3 is a hydrogen atom or a (C1 to C4) alkyl group having no substituent, R4 may be the same or different and is a (C1 to C8) alkoxyl group optionally having a substituent, (C1 to C8) alkylamino group optionally having a substituent, di (C1 to C8) alkylamino group optionally having a substituent or (C1 to C8) alkylaminocarbonyl (C1 to C8) alkylamino group optionally having a substituent, and P is a (C2 to C4) acyl group~~.

7. (Currently amended) The high-molecular weight derivative of camptothecins according to claim ~~6~~ 5, wherein R1 is a methyl group, A is a trimethylene group, R2 is a hydrogen atom, R3 is a dimethylaminomethyl group, R4 is an isopropylaminocarbonylisopropylamino group, and P is an acetyl group.

8. (Currently amended) The high-molecular weight derivative of

camptothecins according to claim ~~6~~ 5, wherein R1 is a methyl group, A is a trimethylene group, R2 is an ethyl group, R3 is a hydrogen atom, R4 is an isopropylaminocarbonylisopropylamino group, and P is an acetyl group.

9. (Cancelled)

10. (Currently amended) A method of producing the high-molecular weight derivative of camptothecins according to any of claims ~~1~~ 5 to 8, comprising combining a carboxylic acid group at the side chain of a copolymer of polyethylene glycol and a polyglutamic acid ~~polymer having a carboxylic acid group at the side chain,~~ with a phenolic hydroxyl group of phenolic camptothecins via an ester bond, using a condensing agent.

11. (Currently amended) An anticancer agent comprising the high-molecular weight derivative of camptothecins according to any of claims ~~1~~ 5 to ~~9~~ 8.